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08/368,776

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER	
UNGAR, S	
ART UNIT	**PAPER NUMBER**
1806 1806	15

DATE MAILED: 11/27/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on Preliminary Amendment of October 29, 1996.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-27 is/are pending in the application.

Of the above, claim(s) 5-15 + 27 is/are withdrawn from consideration.

☑ Claim(s) 19 is/are allowed.

☑ Claim(s) 1-4, 16-18 + 20-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Interview Summary, PTO-413 4 Sheets

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

★ U.S. GPO: 1996-410-238/40050

1. Claims 1-27 are pending in this application. Claims 5-15 and 27 have been withdrawn from further consideration by the examiner, under 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 1-4 and 16 - 26 are currently under prosecution.

2. The response (Paper No. 11) to the restriction requirement of April 2, 1996 has been received. Applicant has elected Group I, claims 1-4 for examination with traverse. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a). In Paper No. 11 applicants added new claims 16-27 believed to belong with Group I. Claims 16-27 are subject to restriction.

3. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

Group I. Claims 16-26 are drawn to isolated nucleic acids encoding MDK1 polypeptides classified in Class 536, subclass 23.1.

Group II. Claim 27 is drawn to a method for detecting the presence of a nucleic acid encoding a MDK1 polypeptide classified in Class 326, subclass 501.

4. The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (i) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed

can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the nucleic acid product as claimed can be used in a materially different process such as affinity chromatography.

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and/or recognized divergent subject matter, restriction for examination purposes as indicated is proper.

6. A telephone call was made to Charles S. Berkman, (619)552-8400 November 13, 1996 to request an oral election to the above restriction requirement, a provisional election was made with traverse to prosecute the invention of Group I, claims 16-26. Affirmation of this election must be made by applicant in responding to this Office action.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the

time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

8. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

Specification

9. The following amendments to the specification are suggested:

1. Page 25 line 9 should be amended to read "Figure 2A shows relevant regions of the nucleotide sequence of";

2. Page 94, line 3 should be amended to read to read "amino acids (SEQ ID Nos 3 and 5, respectively)"; and,

3. Page 94 line 9 should be amended to read "and MDK1.T2 (SEQ ID Nos 11 and 12, respectively)".

Amendment of the specification will clarify the disclosure.

10. The specification on page 25 states that "key amino acids of the catalytic domarin are highlighted in bold italics" in Figure 1. However, Figure 1 shows no highlighed amino acids. Correction is required.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 USC 112 first paragraph, as failing to provide an enabling disclosure.

The claim is drawn to an isolated nucleic acid encoding a MDK1 polypeptide. An MDK1 polypeptide is defined in the specification, on page 8, lines 14-22, as 2 or more contiguous amino acids set forth in a full length amino acid sequence of SEQ ID No: 2 or a functional derivative thereof. The MDK1 polypeptide can be encoded by a full length or any portion of a full-length nucleic acid sequence, so long as functional activity of the polypeptide is retained. Although the functional activity of a MDK1 polypeptide is not defined in the specification, it is assumed for the purposes of this examination that, because MDK1 appears to be a Eph/Eck family receptor tyrosine kinase, functional activity of a MDK1 polypeptide would include tyrosine kinase activity. Applicant has not enabled an MDK1 polypeptide with 2 amino contiguous amino acids that retains functional activity of the plypeptide.

Sajjadi et al., (New Biol. 1991, 3:769-778) teaches that conserved tyrosine kinase domains of Eph/Eck family tyrosine kinases reside in residues 620-890. Protein chemistry is probably one of the most unpredictable areas of biotechnology, For example, replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparing binding, receptor binding and biological activity of the protein. See Burgess et al.(J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. See Lazar

et al. (Molecular and Cellular Biology, 1988, 8:1247-1252). Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. See Tao et al., (J. of Immunol, 1989,143:2595-2601). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein and thus elimination of 268 amino acids could have devastating effects on the functional acitivity of a protein.

Based on the examples set forth in the specification and known to the skilled artisan at the time of filing, one of skill in the art would be forced into undue experimentation to use the claimed invention as a functional MDK1 polypeptide.

Claim 1 is rejected under 35 USC 112, first paragraph, for the reasons set forth in the objection to the specification.

The specification is further objected to under 35 USC 112, first paragraph, and claim 20 is rejected as failing to provide an enabling disclosure.

The claim is drawn to a nucleic acid that encodes a functional derivative of a MDK1 polypeptide, however applicant has not shown that the encoded proteins which have been derivatized are capable of functioning as that which is being disclosed. It is pointed out that the term "derivative" encompasses a variety of definitions, i.e. chemical modification, deletions, truncatins, substitutions conjugation etc. Applicant has not enabled all of these types of modified proteins. The argument applied to claim 1 as set forth above is also

applicable to the further objection to the specification and the rejection of claim 20.

Based on the examples set forth in the specification and known to the skilled artisan at the time of filing, one of skill in the art would be forced into undue experimentation to use the claimed invention as a functional MDK1 polypeptide as claimed.

Claim 20 is rejected under 35 USC 112, first paragraph, for the reasons set forth in the objection to the specification

The specification is further objected to under 35 USC 112, first paragraph as failing to provide an enabling disclosure.

The claim is drawn to a nucleic acid probe for the detection of a MDK1 polypeptide in a sample.

It is well known in the art that nucleic acid probes bind to RNA and DNA as well as to RNA and DNA binding proteins. The specification teaches methods for detecting the presence of MDK1 RNA in a sample by contacting the sample with a nucleic acid probe under conditions such that hybridization occurs (p. 90, lines 7-17). There is no suggestion in the specification that MDK1 is a nucleic acid binding protein or discussion of how to use a nucleic acid probe for the detection of a MDK1 polypeptide. The nucleic acid sequences of Eph/Eck family tyrosine kinase receptors have been well characterized in the art. Analysis of their nucleic acid sequences have not revealed nucleic acid binding domains. Therefore it would be highly unpredictable for a nucleic acid probe to bind to a Eph/Eck family tyrosine kinase receptor polypeptide.

Based on the lack of guidance in the specification and the examples known to the skilled artisan at the time of filing, one of skill in the art would be forced into undue experimentation to use the claimed invention as a probe for detection of a MDK1 polypeptide as claimed.

Claim 2 is rejected under 35 USC 112, first paragraph, for the reasons set forth in the objection to the specification.

12. Claims 1-4,16-18, and 20-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 16-18 and 20-26 are confusing because they recite the name "MDK1" without characterizing the molecular weight or physiological role of the encoded polypeptide. Claiming biochemical products by a particular name given to the product (i.e. MDK1) by workers in the field fails to distinctly claim what that product is. Applicant can obviate this rejection by reciting specific structural or function elements of MDK1 in the claims.

Claim 16 recites a "nucleic acid....having....". It is unclear whether the word "having" is to be interpreted as being closed or open language. This language is confusing because it is not clear whether the nucleic acid "consists" of the sequence set forth in SEQ ID No. 1 whether it comprises sequences set forth in SEQ ID No. 1.

Claim 17 recites "amino acid sequence having .....". It is unclear whether the word "having is to be interpreted as being closed or open language. This language is confusing because it is not clear whether the nucleic acid "consists"

of the sequence set forth in SEQ ID No. 2 or whether it comprises sequences set forth in SEQ ID No. 2.

Claim 18 recites a "nucleic acid....having....". It is unclear whether the word "having" is to be interpreted as being closed or open language. as being closed or open language. This language is confusing because it is not clear whether the nucleic acid "consists" of the sequence set forth in SEQ ID Nos. 3 or 4 whether it comprises sequences set forth in SEQ ID Nos. 3 or 4.

Claim 20 is confusing because it recites a nucleic acid that "encodes a functional derivative of the full length MDK1 amino acid". It is not clear what is meant by a functional derivative, does this mean that the MDK1 derivative is capable of binding ligand or capable of phosphorylation activity or is it capable of stimulating cell growth and proliferation or all or none of these functions?

Claims 21-25 recite a "sequence encoding the MDK1". The claim is confusing because it is not clear what is meant by MDK1, is this the MDK1 polypeptide or is it the MDK1 receptor tyrosine kinase?

Claim 26 is confusing because it recites "a genetically engineered host cell". It is not clear what is meant by a genetically engineer host cell, is the host cell genetically engineered before transfection or transformation or does it become genetically engineered only after it contains a genetically engineered vector?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-4 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sajaddi et al (New Biol, 1991, 3:769-778).

The claims are drawn to: (1) an isolated or purified nucleic acid encloding a MDK1 polypeptide; (2) a nucleic acid probe for the detection of a MDK1 polypeptide; (3) a recombinant nucleic acid encoding a MDK1 polypeptide and a vector effective to initiate transcription in a host cell; and (4) a recombinant nucleic acid comprising a transcriptional region functional in a cell, a sequence complimentary to an RNA sequence encoding a MDK1 polypeptide and a transcriptional termination region functional in a cell. For purposes of this examination, the nucleic acid probe of claim 2 is assumed to be for the detection of a MDK1 nucleic acid in a sample. A MDK1 polypeptide is defined as set forth above.

Sajaddi et al teach: (1) an isolated cDNA that encodes a receptor tyrosine kinase (see Abstract p. 769) that has a nucleic acid sequence with 46.4% sequence identity with SEQ ID NO: 2 with numerous examples of 2 or more contiguous amino acids as set forth in the full length amino acid sequence of SEQ ID No: 2 (see Locus MUSMEK4, attached at the back of Sajaddi et al); (2) a specific cek4 probe used to screen for and isolate the receptor tyrosine kinase cDNA taught by Sajaddi et al (p. 770 para 2); (3) a recombinant nucleic acid encoding the receptor tyrosine kinase inserted into pBluescript vectors and subcloned under standard procedures; and (4) the sequences of both produced

strands were analyzed (p. 777, para 4). For your information, it is noted that WO9300425 and Wicks et al.,(PNAS, 89:1611-1615, 1992) also teach isolated nucleic acids encoding a tyrosine kinase with 46.8% sequence identity with SEQ ID NO:2 with numberous examples of 2 or more contiguous as set forth in the full length amino acid sequence of SEQ ID No:2 and could be cited as references in a rejection of claim 1 under USC 102(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

13. Claims 21-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Sajaddi et al (New Biol, 1991, 3:769-778) as applied to claims 1-4 and further in view of US Patent No. 5,521,295, and US Patent No. 5,504,000.

The claims are drawn to a nucleic acid sequence encoding the MDK1 extracellular domain, transmembrane domain, kinase domain, intracellular

domain and/or a nucleic acid encoding two or more of the domains selected from the group consisting of the MDK1 extracellular, transmembrane, kinase or intracellular domain and a genetically engineered host cell containing a nucleic acids selected from the group of nucleic acids encoding domains or full length sequences of MDK1. It is assumed for purposes of examination that MDK1 is the MDK1 receptor tyrosine kinase.

Sajjadi et al teach, as set forth above, an isolated cDNA that encodes a receptor tyrosine kinase that has a nucleic acid sequence with numberous examples of 2 or more contiguous amino acids as set forth in the full length amino acid sequence of SEQ ID No: 2. Further, Sajjadi et al teach that a number of receptor tyrosine kinases have been shown to mediate cellular growth, differentiation and mitogenic activities (p. 769, para 1) however, the ligands, substrates and mechanisms of action of most receptor tyrosine kinases remain unknown and therefore characterization of new members of this family should provide important insights into the mechanisms underlying cellular growth control pathways (p. 769, para 2). Sajjadi et al do not teach isolated, enriched or purified domains of the isolated cDNA.

US Patent No. 5,521,295 teaches a method of studying the mechnaisms of receptor activation and signaling by constructing syntheitc receptor molecules known as hybrid receptors. Such receptors typically possess the extracellular domain of one naturally occurring receptor and the intracellular domain of another naturally occurring receptor (col 2, lines 48-55). Hybrid receptors have been produced that consist of the extracellular domain of EGFR and the intracellular domain of PDGFR, both receptors are members of the protein

tyrosine kinase family (col 3, lines 21-26). Heterologous hybrid receptors have been generated with the extracellular domain being from EGFR and the intracellular domain from a receptor of a different family.(col 3, lines 42-51). Interfamilial hybrid receptors provide a means for obtaining information about newly identified receptors with unknown ligands. For example, the extracellular domain of a newly identified receptor may be linked to an intracellular domain of a receptor with a known signal transduction mechanism. Various ligands can be tested to identify those that bind to the extracellular domain of the hybrid and are capable of transmitting a signal (col 3, line 62-col 4 line 2). In addition, ligands that bind to the receptor can be screened to evaluate their potential for increasing or decreasing receptor activity (col 7, lines 38-45). The intracellular receptor DNA sequence may be a fragment of a known sequence from which it is derived ((col 8, lines 12-29). The preferred intracellular domains are those with a known and assayable signaltransduction mechanism or activity such as tyrosine phosphorylation as seen in EGFR (col 8, lines 43-50). The transmembrane domain sequence of the hybrid receptor may be obtained from any source. Typically it will be selected from the same receptor as either the intracellular domain or the extracellular domain. The transmembrane domain may also be selected from a receptor that is a member of a separate and distinct group from either the intracellular or extracellular domain receptor. While the main purpose of the transmembrane domain appears to be to anchor the receptor into the membrane, this domain may also be important in certain receptors for signal transduction (col 8, line 62-col 9 line 5) The hybrid receptors of this invention are typically prepared using recombinant DNA technology. A DNA

construct containing the DNA sequences of the selected intracellular, extracellular and transmembrane domains is prepared, usually by isolating the desired cDNA sequences for each domain of the hybrid receptor, using methods well known in the art. (col 9, lines 10-16). After the DNA sequences for each of the domains have been obtianed in suitable quantities, they are ligated in the proper orientation, thereby producing a single DNA construct encoding the intracellular, transmembrane and extracellular domains of the desired hybrid receptor (col 9, lines 27-31). The DNA encoding the hybrid receptor will typically be placed into a vector for aimplification and for expression in the host cells (col 9, lines 46-48).

US Patent No. 5,504,000 teaches the construction of a chimeric protein tyrosine kinase with the src tyrosin kinase domain fused to the extracellular and transmembrane domains of CD4. The src tyrosine kinase portion of the chimeric protein may be full length or a fragment thereof (col 6, lines 32-38). The invention provides an isolated DNA encoding encoding an src tyrosine kinase (col 6, lines 60-64).

The specification teaches a nucleic acid encoding an MDK1 polypeptide defined as 2 or more contiguous amino acids set forth in a full length amino acid sequence of SEQ ID No: 2 or a functional derivative thereof that retains functional activity of the polypeptide. The nucleic acid encoding the polypeptide of Claim 1 appears to be the same as the nucleic acid taught by Sajjadi et al. The patentability of the claimed MDK1 polypeptide depends on whether the polypeptide was known in the art and therefore, the burden is upon the

applicants to establish a patentable distinction betweened the claimed and referenced tyrosine kinease receptor.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the nucleic acid of Sajjadi et al in the method of US Patent No. 5,521,295 to produce a nucleic acid sequence encoding the MDK1 extracellular domain, transmembrane domain, kinase domain, intracellular domain and/or a nucleic acid encoding two or more of the domains selected from the group consisting of the MDK1 extracellular, transmembrane, kinase or intracellular domain and a genetically engineered host cell containing the nucleic acid because US Patent No. 5,521,295 specifically teaches that hybrid receptors can be synthesized from isolated fragments of DNA encoding different receptors and nucleic acids can be amplified by being placed in a vector and then expressed in a host cell and US Patent No. 5,521,295 specifically teaches that intracellular DNA sequence may be a fragment of a known sequence from which it is derived and US Patent No.5,504000 specifically teaches that hybrid receptors may be constructed with a src tyrosine kinase intracellular domain. One of ordinary skill in the art would have been motivated to substitute the nucleic acid of Sajjadi et al in the method of US Patent No. 5,521,295 to produce a nucleic acid sequence encoding the MDK1 extracellular domain, transmembrane domain, kinase domain, intracellular domain and/or a nucleic acid encoding two or more of the domains selected from the group consisting of the MDK1 extracellular, transmembrane, kinase or intracellular domain and a genetically engineered host cell containing the nucleic acid because Sajjadi et al specifically teach that: (1) a number of

receptor tyrosine kinases have been shown to mediate cellular growth, differentiation and mitogenic activities; (2) the ligands, substrates and mechanisms of action of most receptor tyrosine kinases remain unknown; and (3) that characterization of new members of this family should provide important insights into the mechaism of cell growth, diffrentiation and mitogenic activities and because US Patent No. 5,521,295 specifically teaches that receptor tyrosine kinase domains have been used in the construciton of both interfamilial and heterogeneous hybrid receptors that provide a means for identifying ligands and/or functions of newly identified receptors.

14. Claim 19 appears to be free of the art.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached at (703) 308-2731. The fax phone number for this Art Unit is (703) 308-4065.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
November 22, 1996

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800